Massachusetts
Institute of
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Cancer as an evolutionary process

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Main points

1. Cancer is an evolutionary process

2. Cancer genomics allows to look under the hood of this process

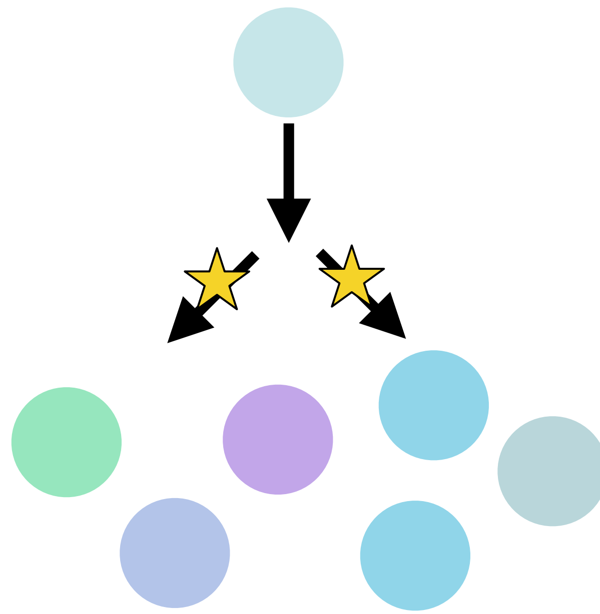
3. Treating cancer using its own evolutionary mechanisms

Evolution

mutations

diversity

selection

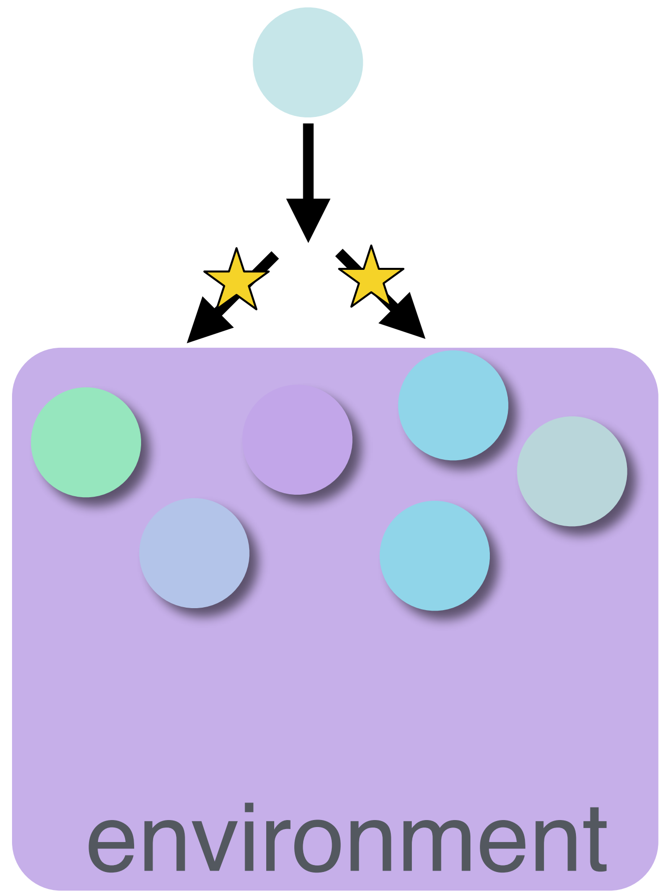


Evolution

mutations

diversity

selection



Evolution

mutations

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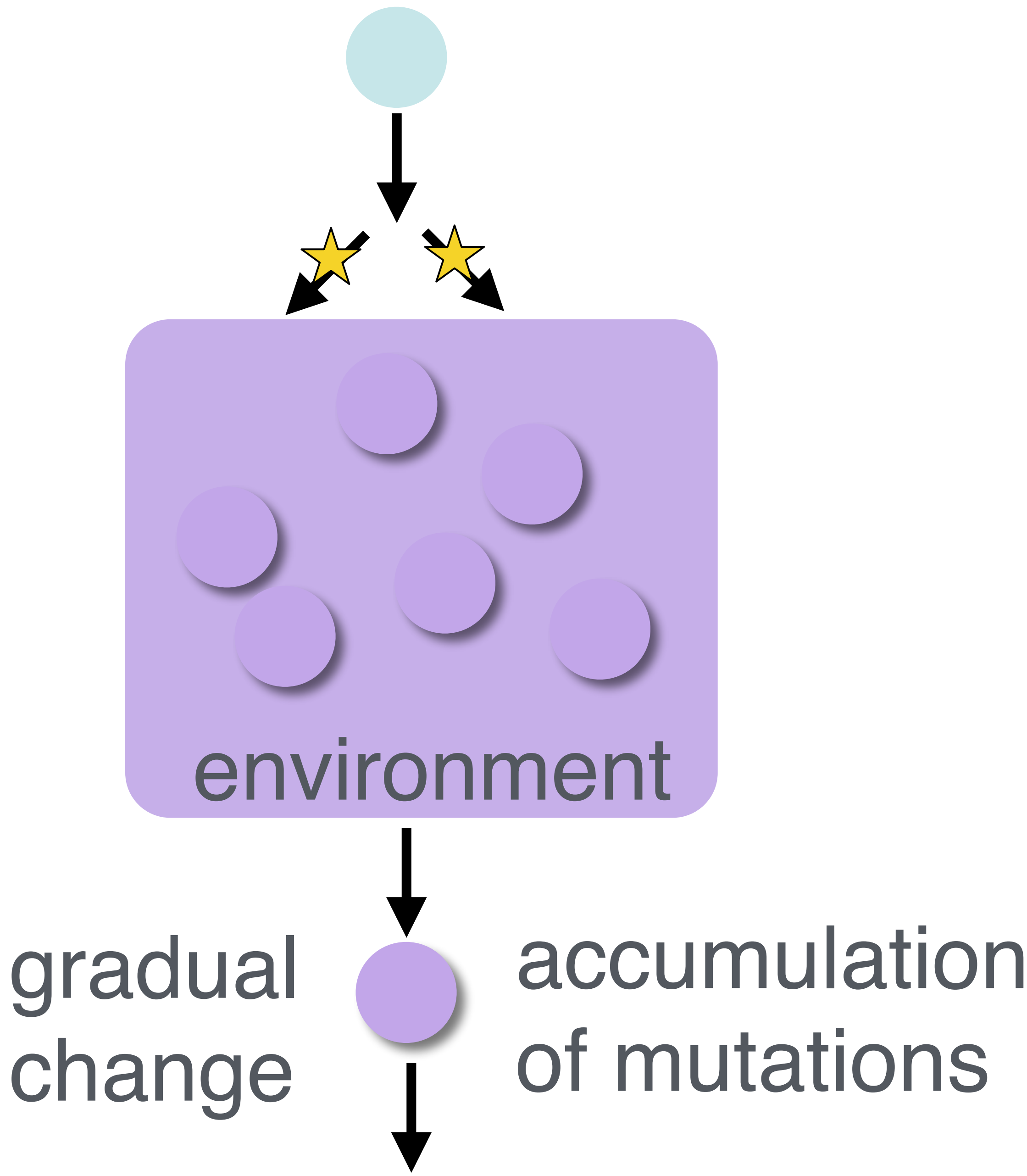
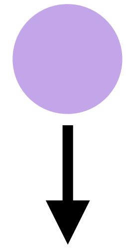
selection



Mutant is new normal



new phenotype
is acquired

mutations

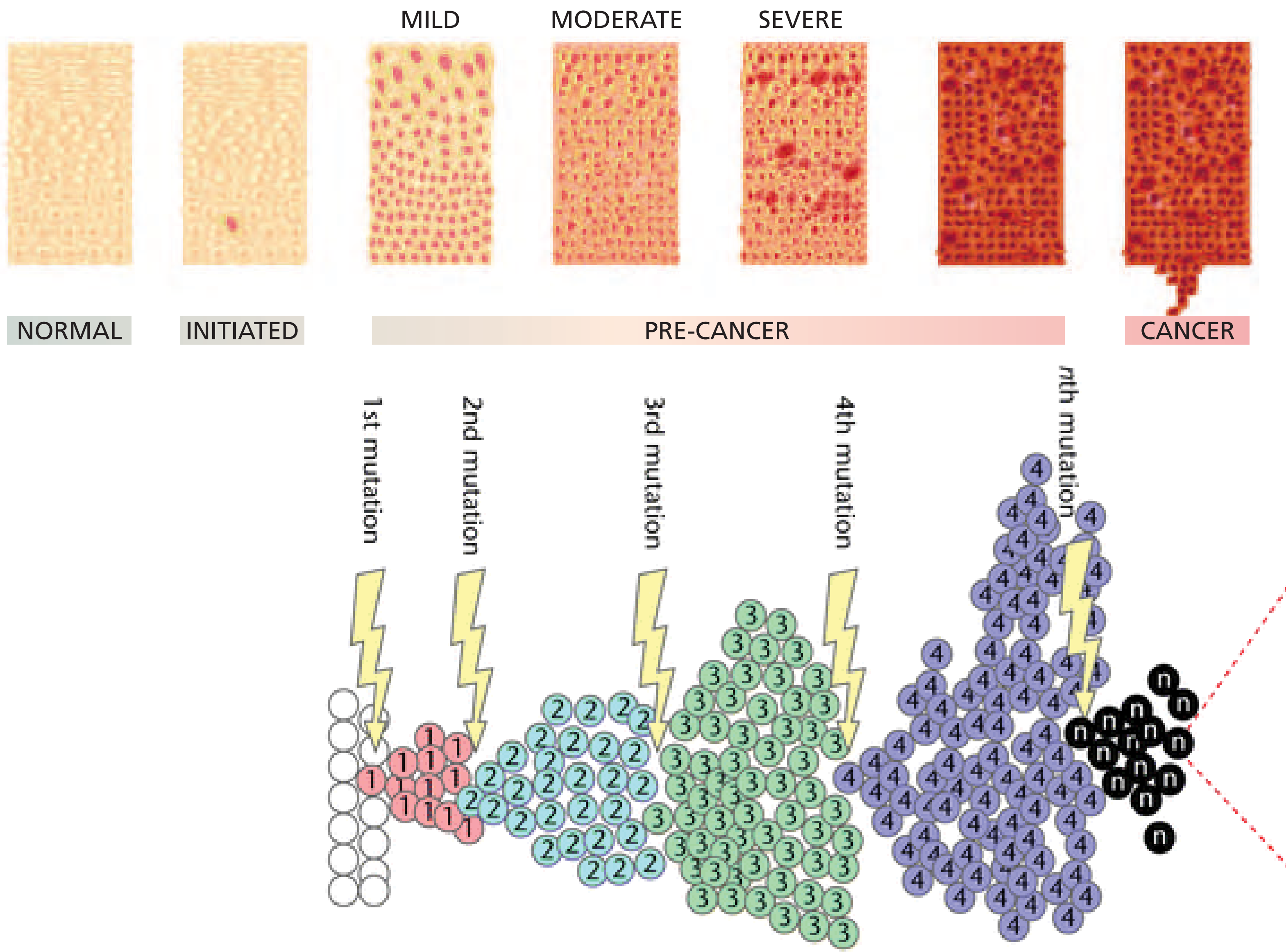
diversity

selection

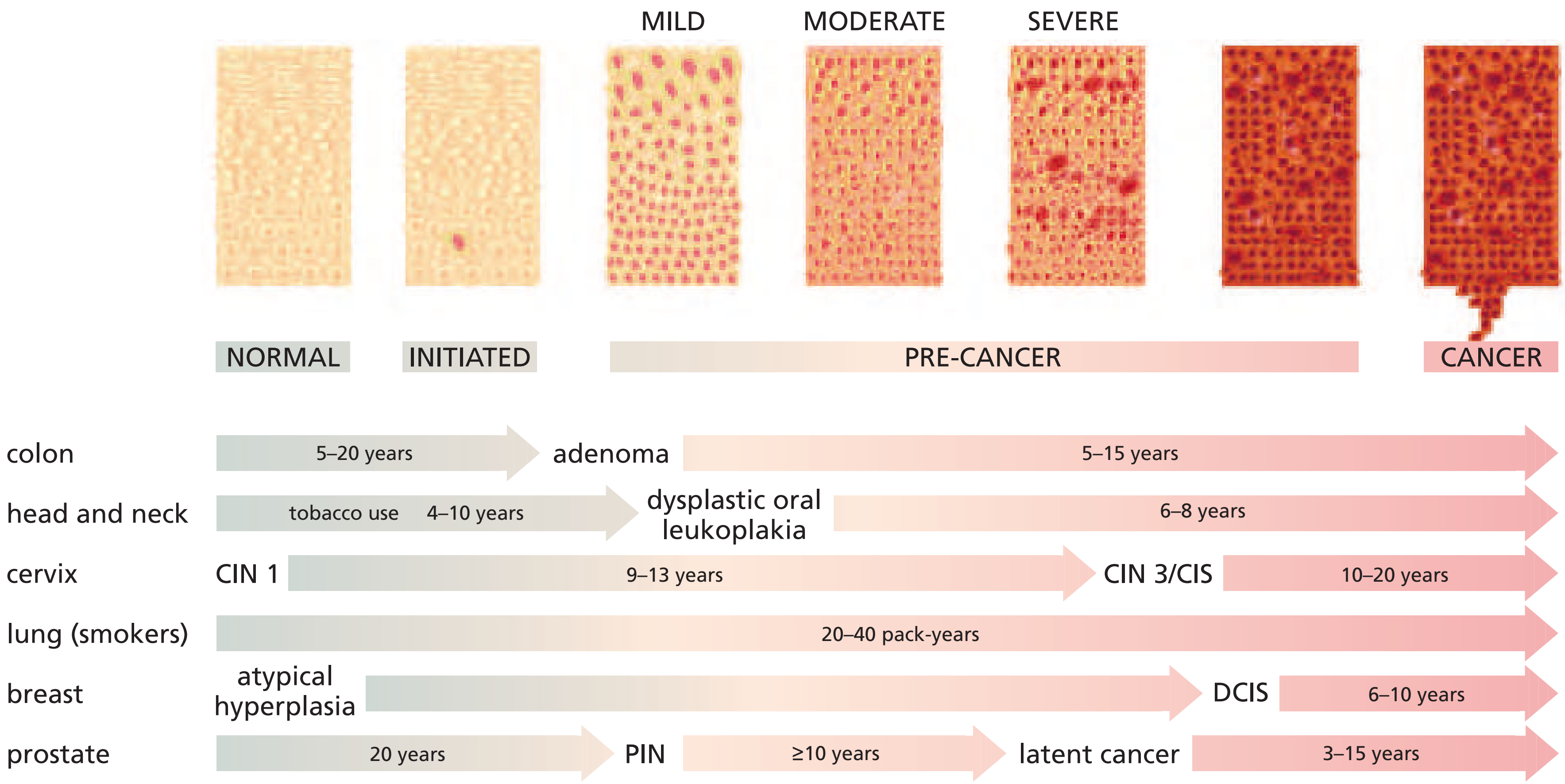
gradual
change

accumulation
of mutations

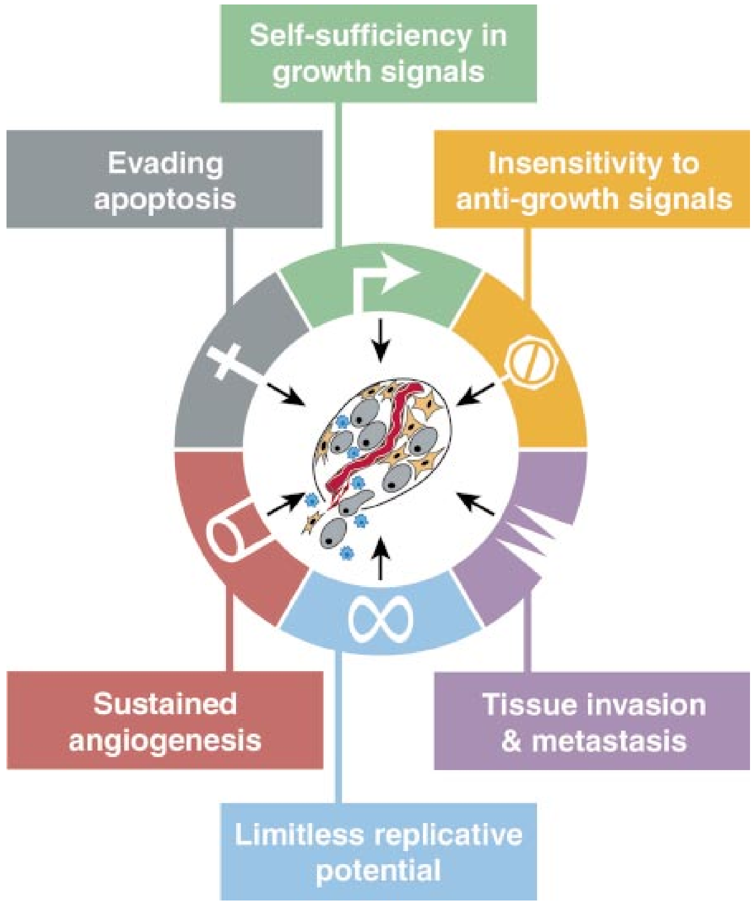
Cancer = evolution



Cancer = evolution



Acquired phenotypes of cancer



Cell, Vol. 100, 57–70, January 7, 2000, Copyright ©2000 by Cell Press

The Hallmarks of Cancer

Douglas Hanahan* and Robert A. Weinberg†

Acquired phenotypes of cancer acquired *mutations*

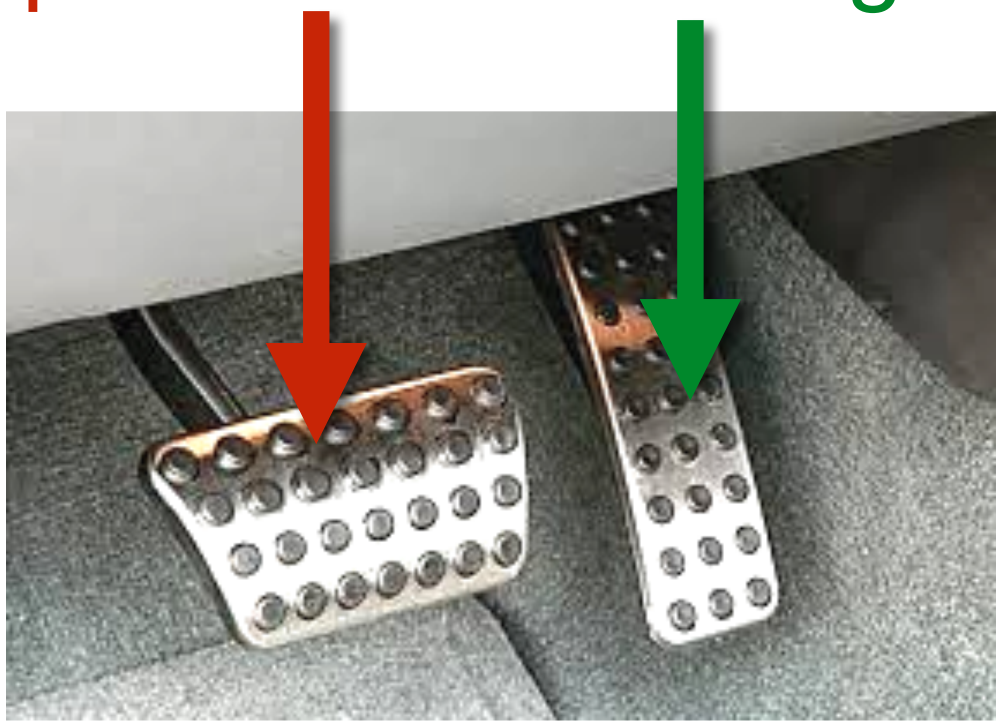
Mutation targets

tumor suppressors and oncogenes

Acquired phenotypes of cancer acquired *mutations*

Mutation targets

tumor suppressors and oncogenes



Acquired phenotypes of cancer acquired *mutations*

Mutation targets
tumor suppressors and oncogenes

Mutation targets

tumor suppressors and oncogenes

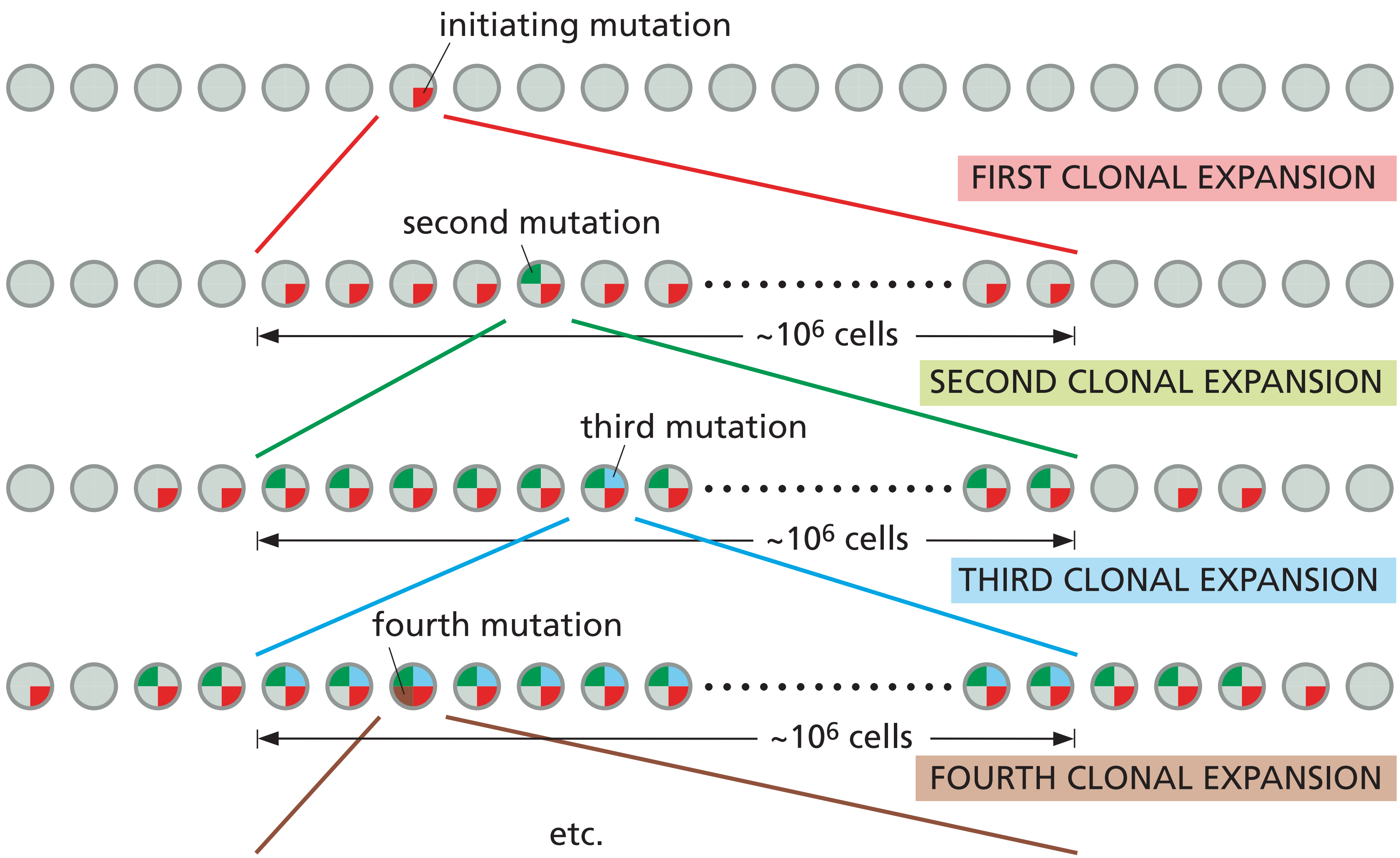
[drivers]

Oncogenes and tumor suppressors **[drivers]**

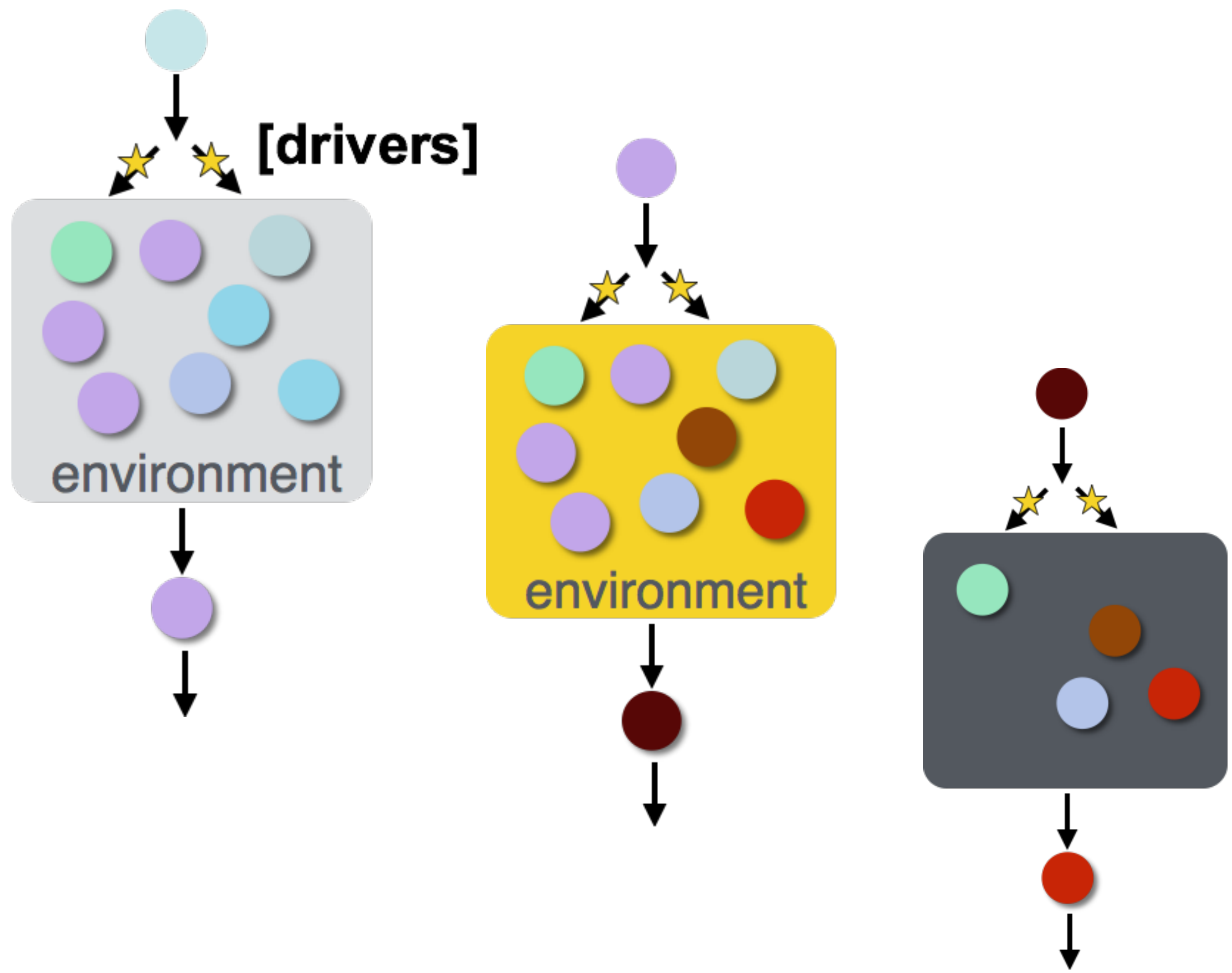
- Oncogenes -- need to be activated
  - by mutations (within a gene or regulatory regions)
  - by chromosomal alterations
  - overexpression/modifications

- Tumor suppressors -- need to be inactivated
  - mutations, chromosomal loss, modifications

Cancer: series of **driver** mutations



Cancer: is hard to stop because it's an evolutionary process



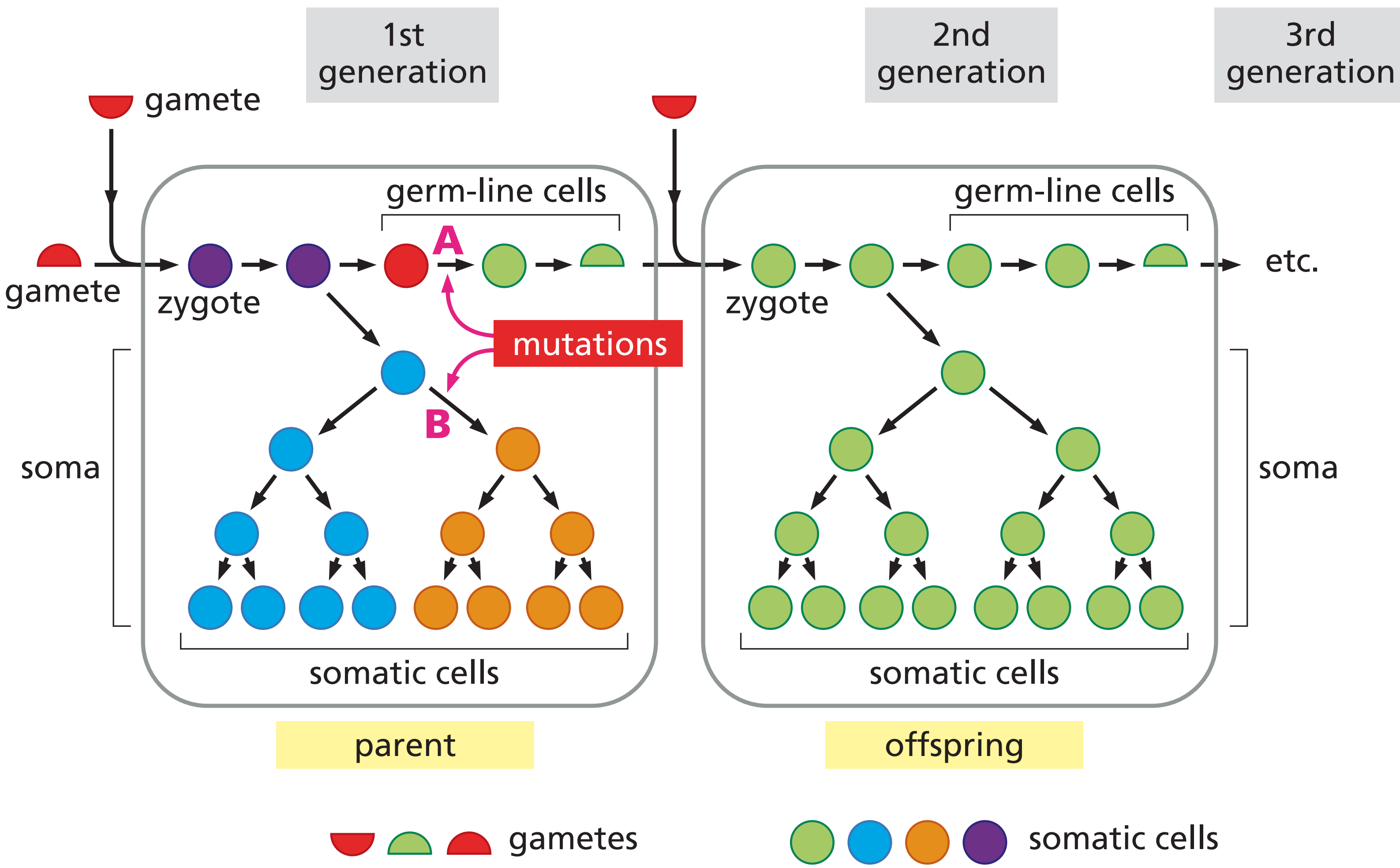
Main points

1. Cancer is an evolutionary process

2. Cancer genomics allows to look under the hood of this process

3. Treating cancer using its own evolutionary mechanisms

Mutations: germline and somatic



Cancer genomics

- Get a sample of **cancer** => sequence
- Get a sample of **normal tissue**
  (from the same patient) => sequence

Cancer

Normal

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Cancer

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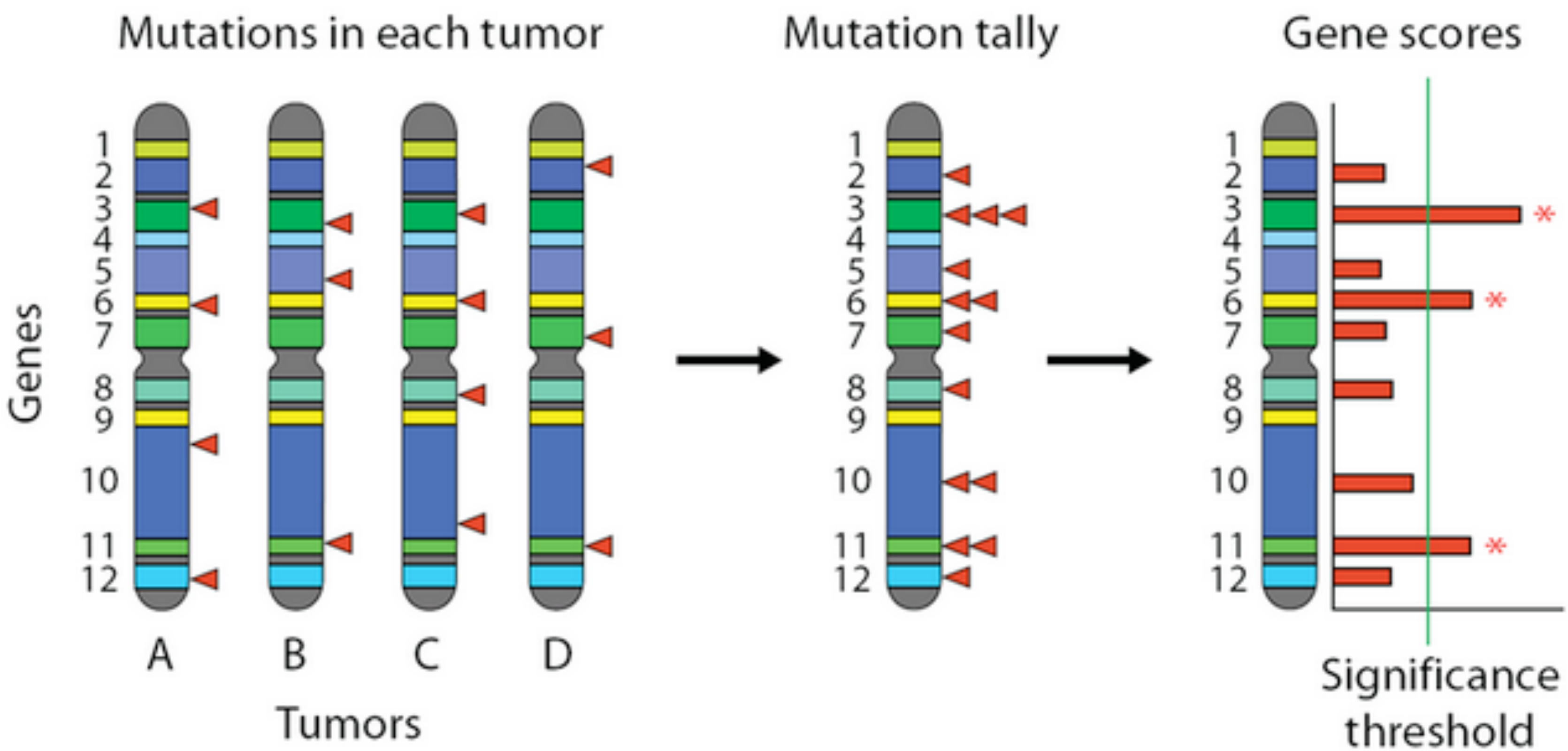
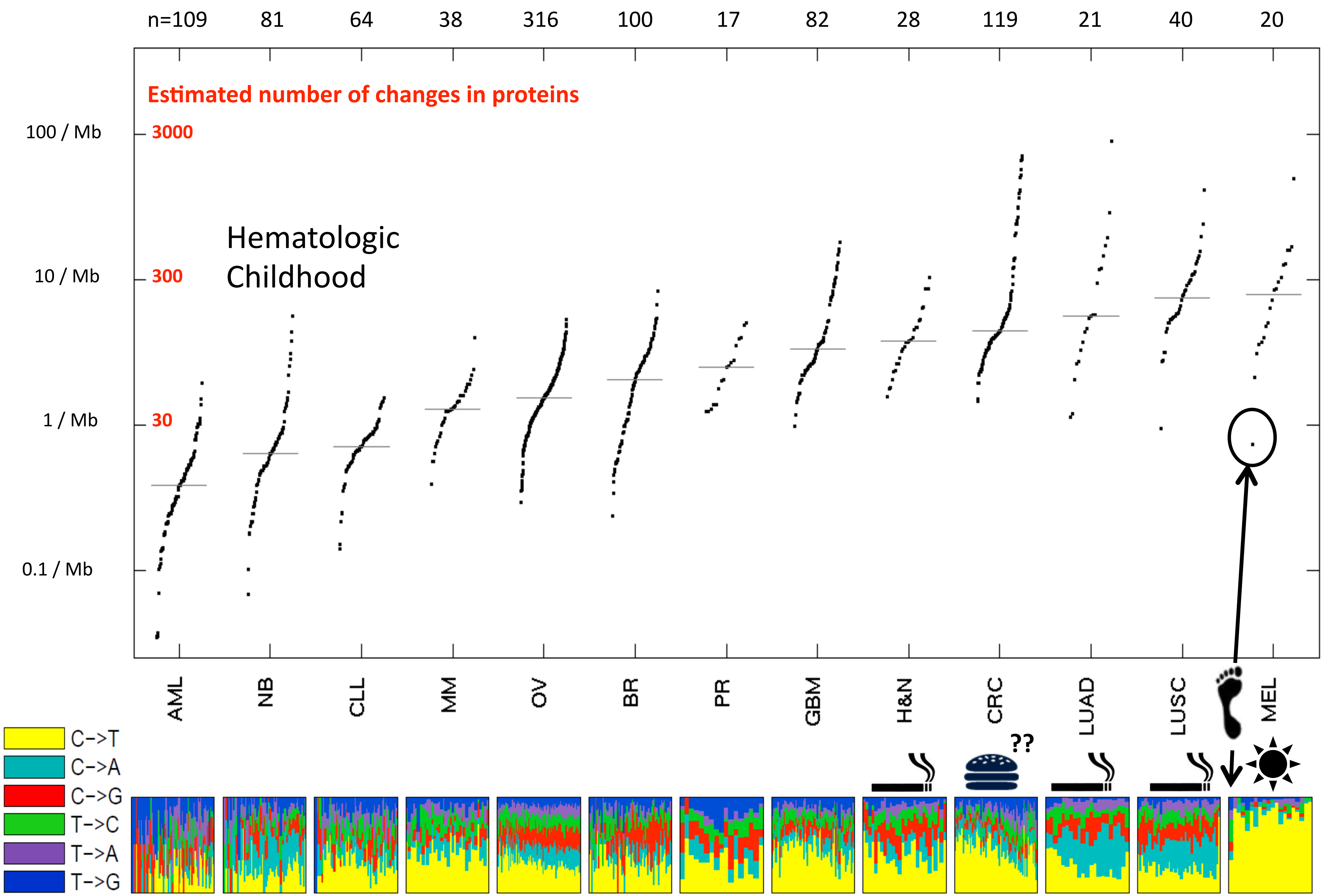
Finding **driver** events



Rates of somatic mutation vary across cancers: [G.Getz]



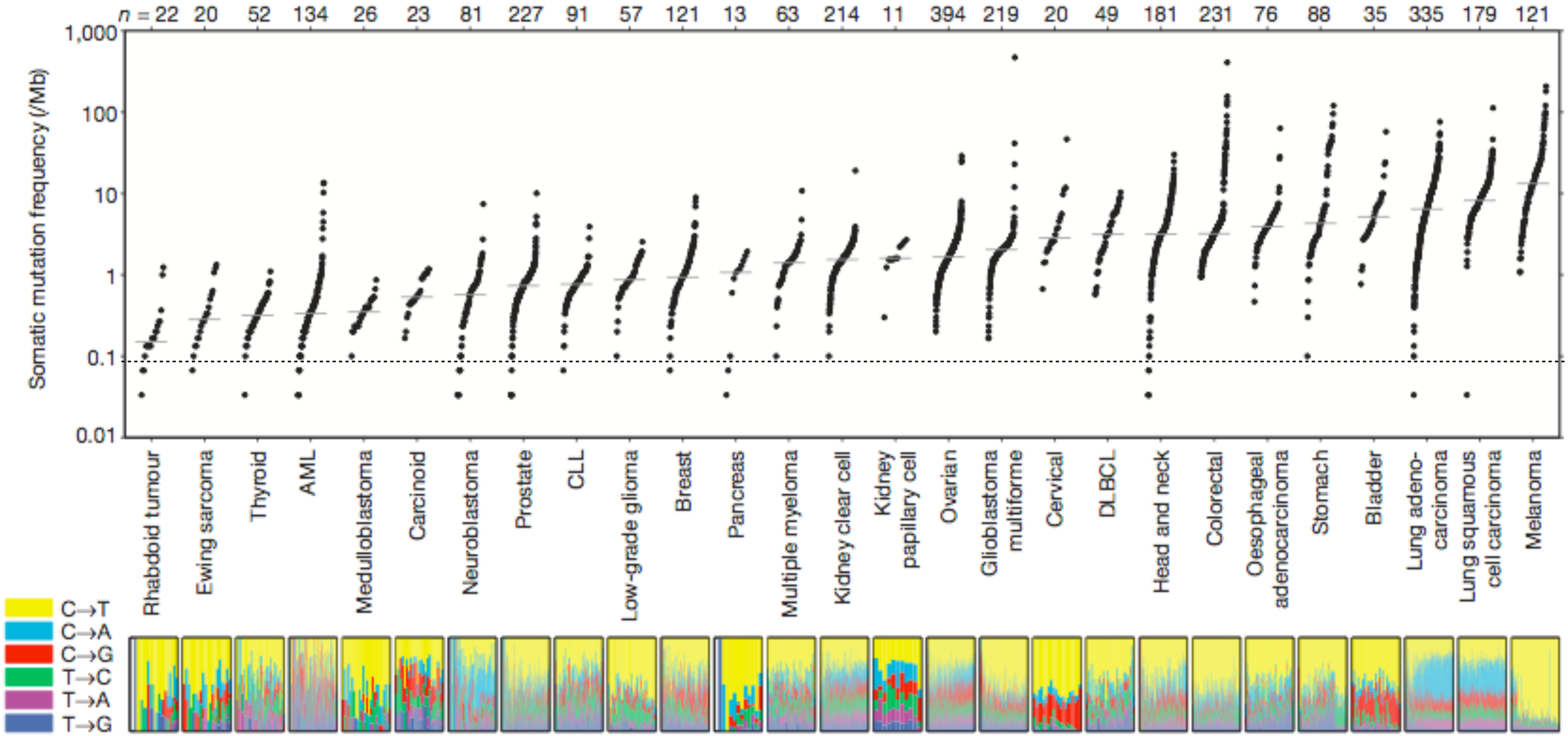


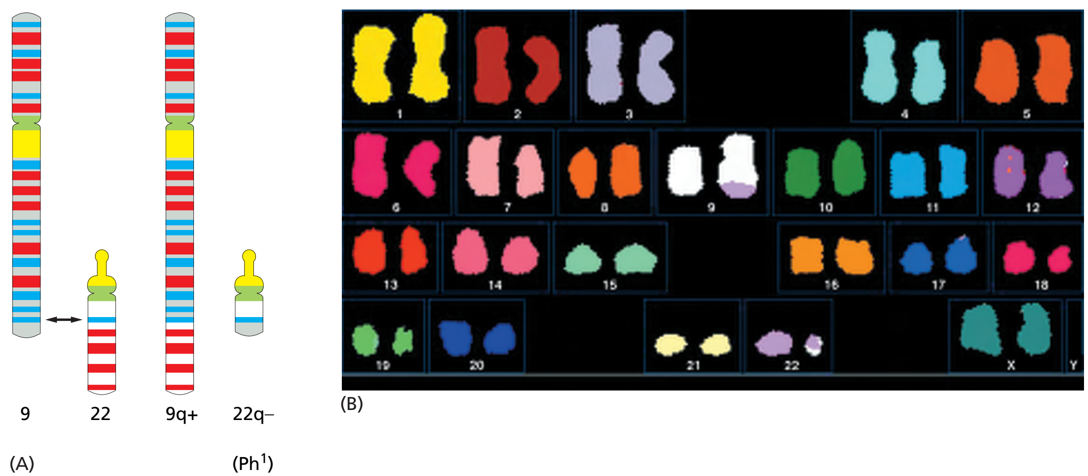
Figure 1 | Somatic mutation frequencies observed in exomes from 3,083 tumour–normal pairs. Each dot corresponds to a tumour–normal pair, with vertical position indicating the total frequency of somatic mutations in the exome. Tumour types are ordered by their median somatic mutation frequency, with the lowest frequencies (left) found in haematological and paediatric tumours, and the highest (right) in tumours induced by carcinogens such as tobacco smoke and ultraviolet light. Mutation frequencies vary more than 1,000-fold between lowest and highest across different cancers and also within several tumour types. The bottom panel shows the relative proportions of the six different possible base-pair substitutions, as indicated in the legend on the left. See also Supplementary Table 2.

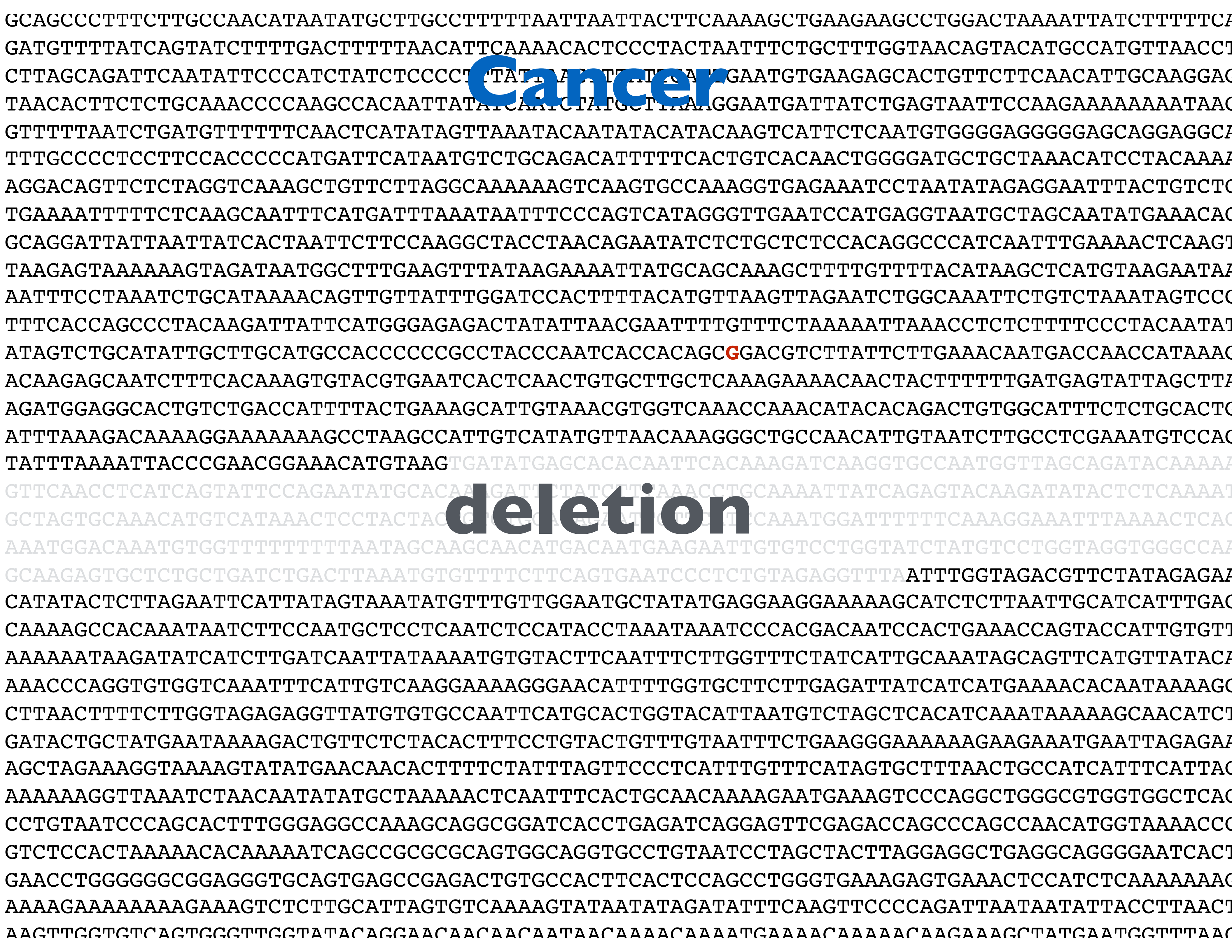
M. Lawrence et al *Nature* 2013

Cancer genomics

- Whole-genome sequences (cancer vs normal)
- Whole-exome sequences (cancer vs normal)
- Copy-number alterations

Chromosomal alterations




Cancer
deletion

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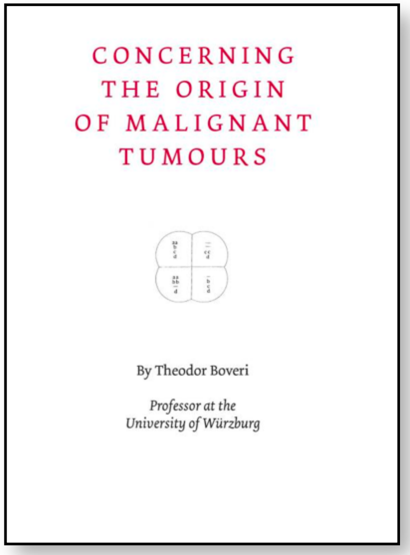
Cancer

amplification

Somatic Copy Number Alterations (SCNAs)



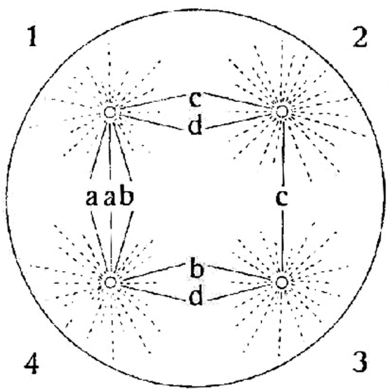
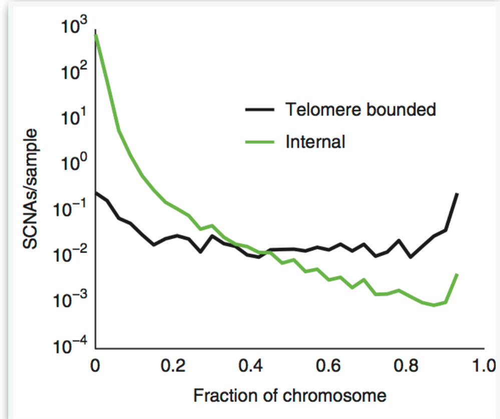
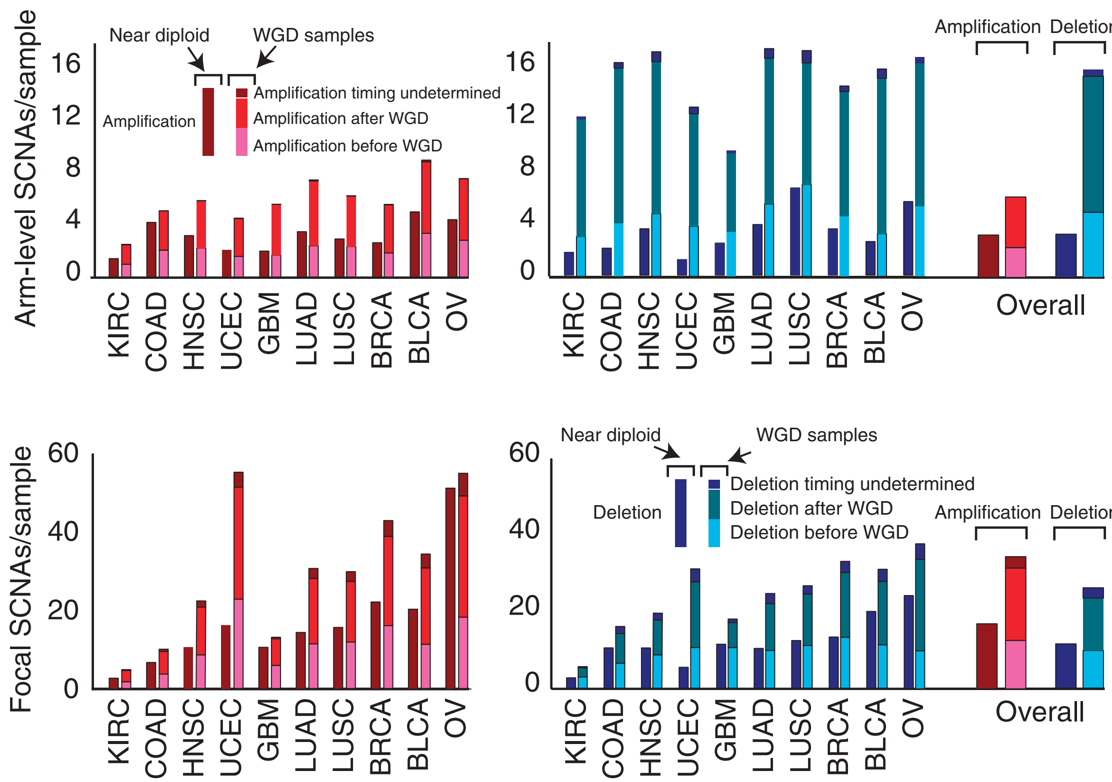
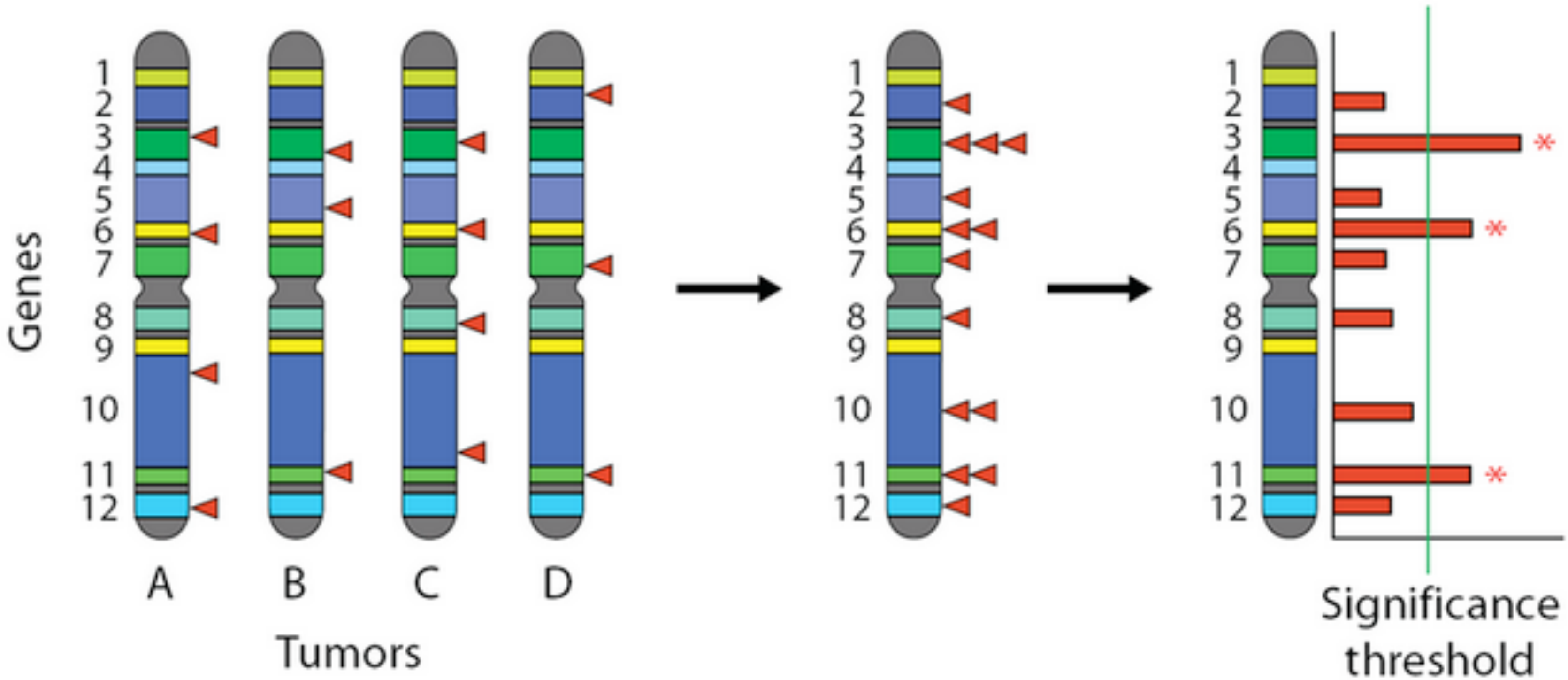


Fig. A.





Finding **oncogenes** and **tumor suppressors**



Deletions Amplifications

tumor suppressors and oncogenes

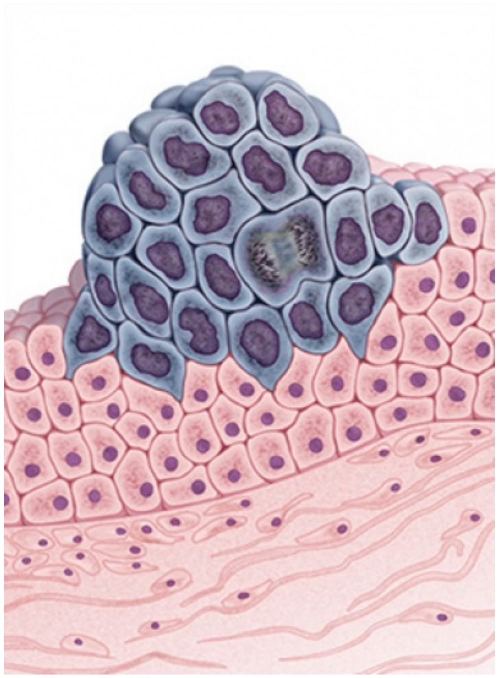
Cancer genomics

Finding new oncogene and tumor suppressors

Whole mutational landscape of cancer

Precision medicine:

mutations in each patient



Main points

1. Cancer is an evolutionary process

2. Cancer genomics allows to look under the hood of this process

3. Treating cancer using its own evolutionary mechanisms

Cancer genomics

100-400 amino acid substitutions

10-40 chromosomal alterations

2-5 drivers

the rest are passengers

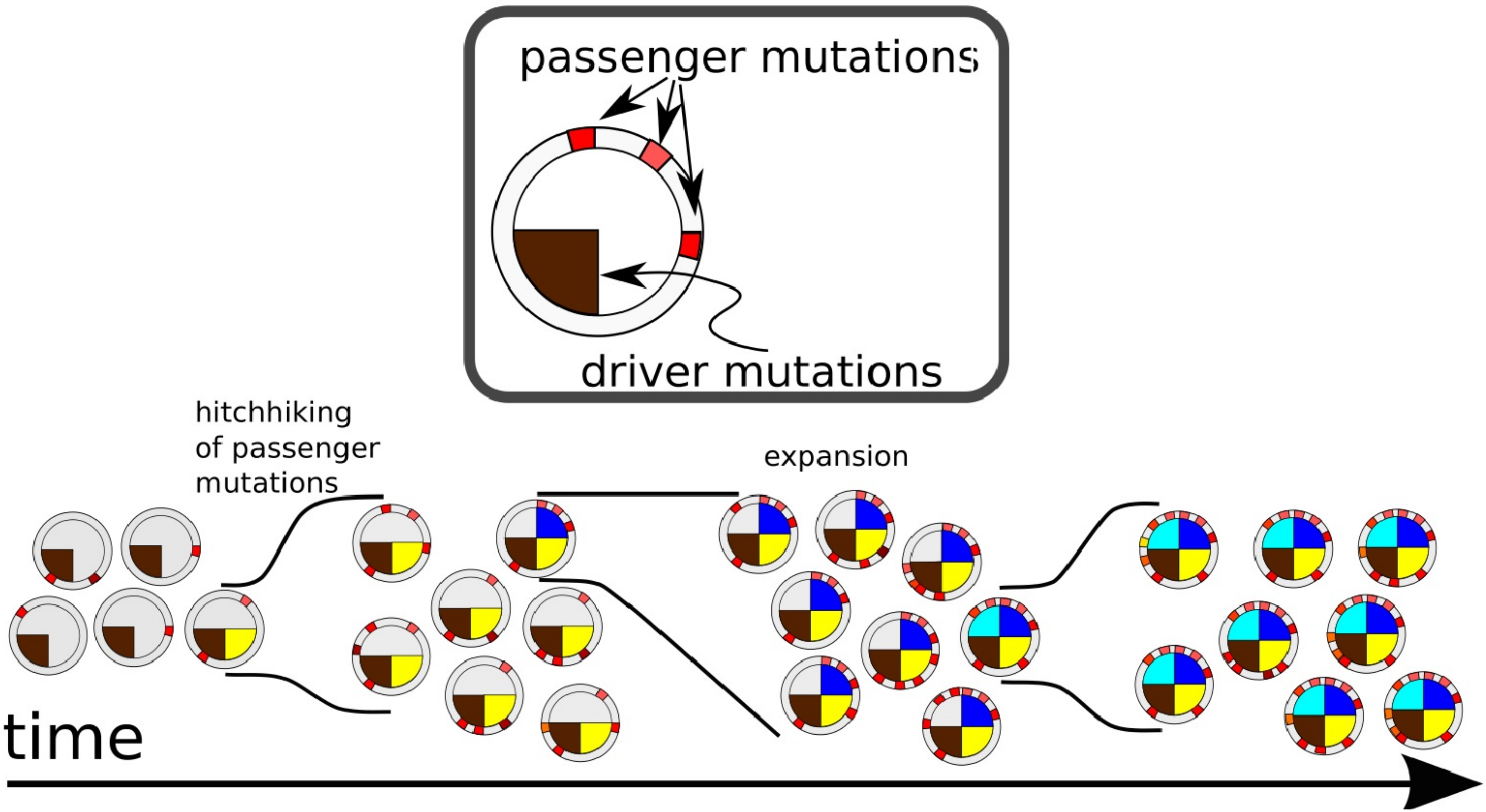
Can some passengers

... be deleterious to cancer cells?

... affect progression?

Are cancers weighted down by passengers?

Passengers hitchhike of drivers

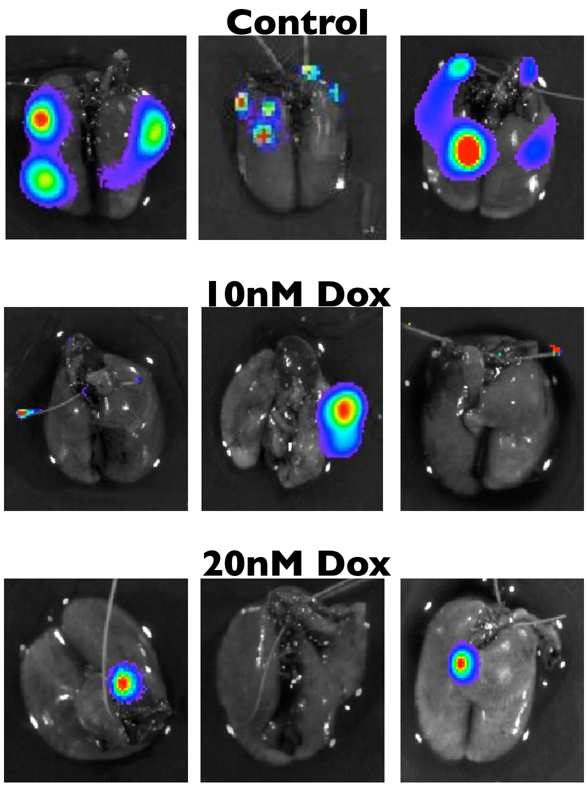


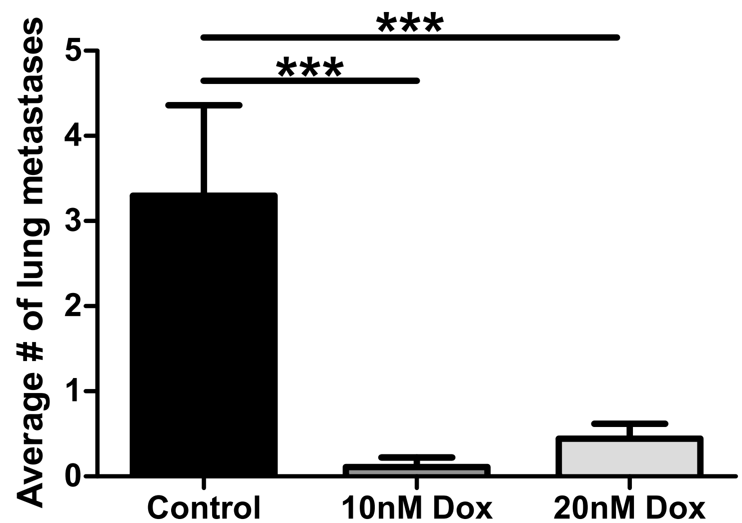
Passengers hitchhike to fixation

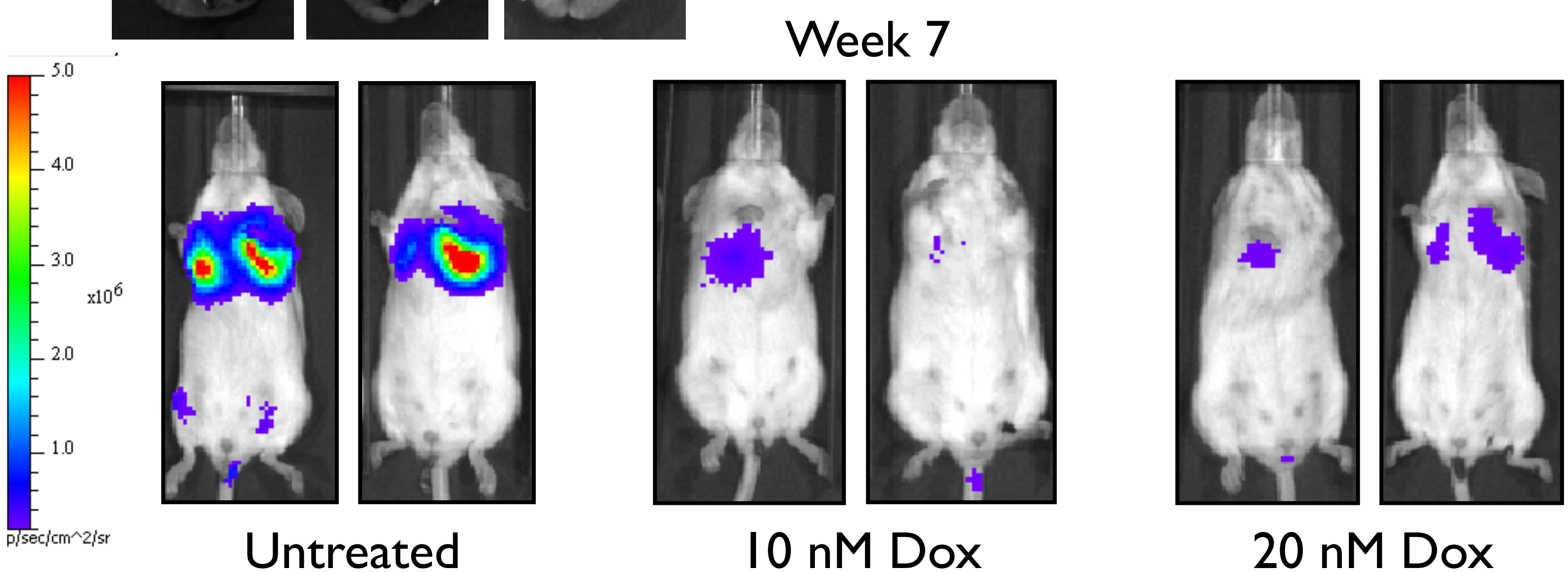
Hitchhiking passengers

Neutral | or | deleterious

Passanger load negatively correlates with metastasis





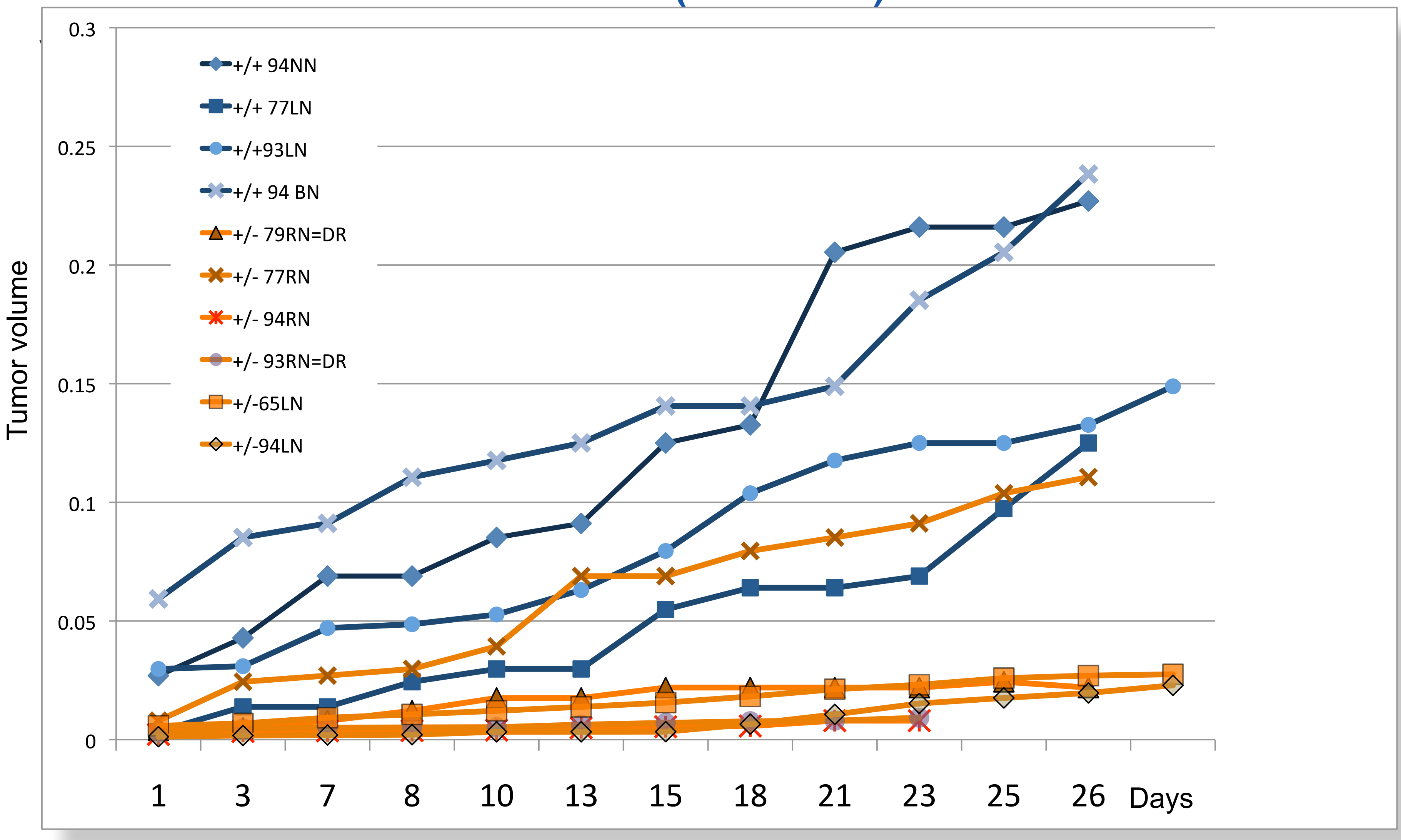


Passengers slowdown cancer

New Experiment: Her2+ breast cancer mouse model:

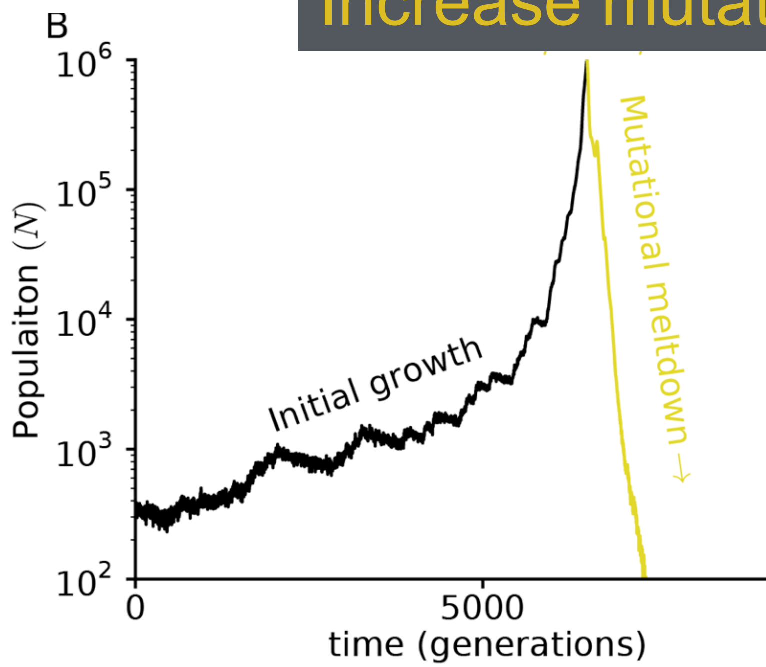
mildly elevated mutation rate (H2AX+/-)

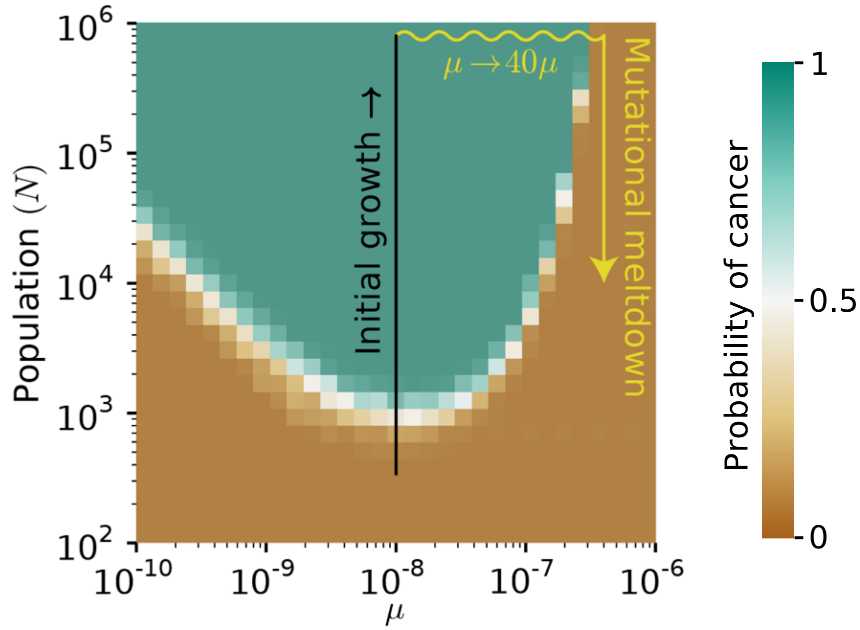
normal mutation rate (control)



Passenger-based treatment

Increase mutation rate





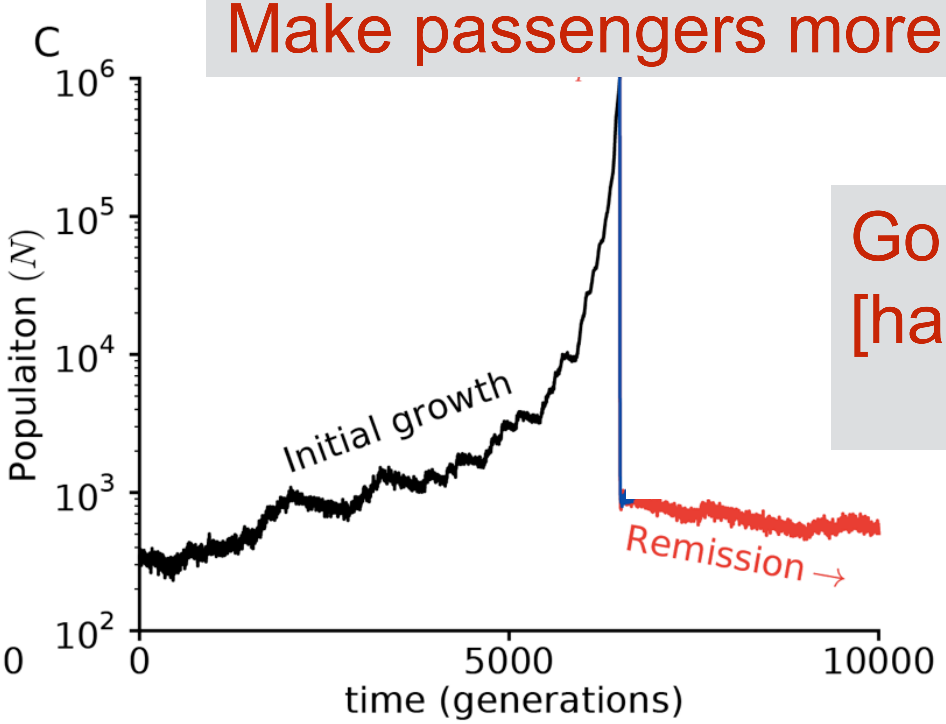
Mutagenic chemo

- requires very high mutation rate

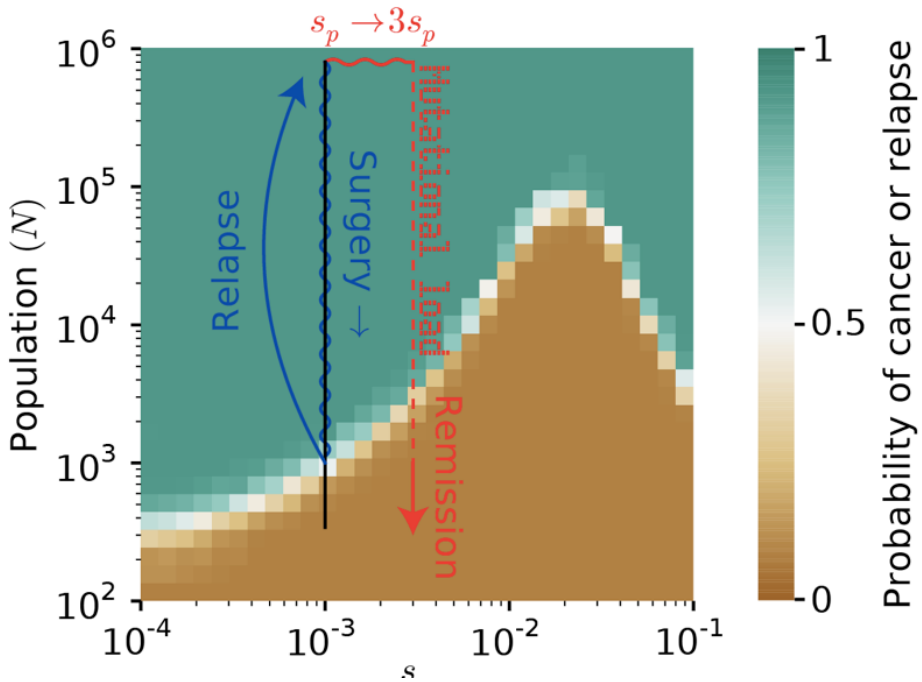
- likely relapse

Passenger-based treatment

Make passengers more damaging



Going with evolution, not against it
[hackers lingo:
passneger load is an **exploit**]



Response to immunotherapy is associated with mutational load

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

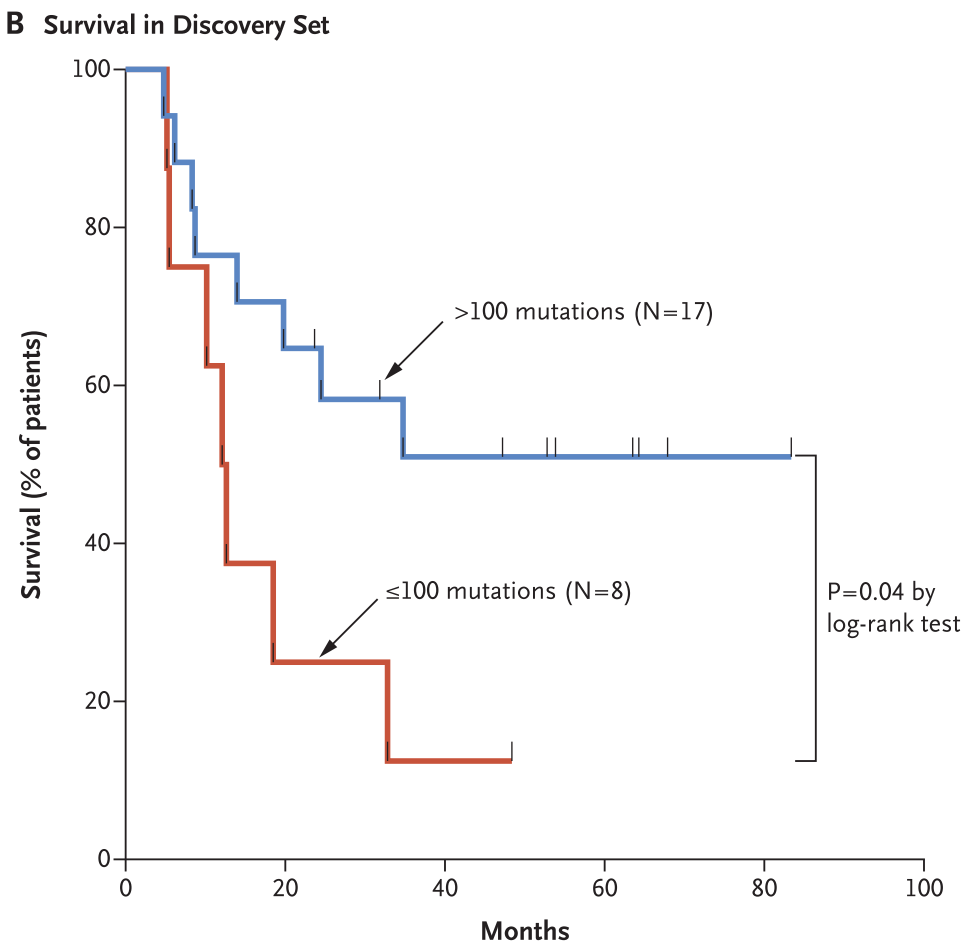


Figure 2. **Mutational Landscape of Tumors According to Clinical Benefit from Ipilimumab Treatment.**

Genetic Basis for Clinical Response to CTLA-4 Blockade in Melanoma

Alexandra Snyder, M.D., Vladimir Makarov, M.D., Taha Merghoub, Ph.D., Jianda Yuan, M.D., Ph.D., Jesse M. Zaretsky, B.S., Alexis Desrichard, Ph.D., Logan A. Walsh, Ph.D., Michael A. Postow, M.D., Phillip Wong, Ph.D., Teresa S. Ho, B.S., Travis J. Hollmann, M.D., Ph.D., Cameron Bruggeman, M.A., Kasthuri Kannan, Ph.D., Yanyun Li, M.D., Ph.D., Ceyhan Elipenahli, B.S., Cailian Liu, M.D., Christopher T. Harbison, Ph.D., Lisu Wang, M.D., Antoni Ribas, M.D., Ph.D., Jedd D. Wolchok, M.D., Ph.D., and Timothy A. Chan, M.D., Ph.D.

Work in progress…

1. Passenger mutations can be damaging!
2. Passenger load is a potential biomarker of response to chemo- and immuno- therapy
3. Passengers may be responsible for other cancer phenotypes

NEED :: More patient info + genotypes (PLM?)

Main points

1. Cancer is an evolutionary process
2. Cancer genomics allows to look under the hood of this process
3. Treating cancer using its own evolutionary mechanisms

MIT Physical Sciences-Oncology Center

Chris McFarland

Stanford University

Kirill Korolev,

Boston University

Experiments

Julia Yaglom

Michael Sherman

BU Medical School

Metastatic potential

MOFFITT CANCER CENTER

David Morse,

Jacob Scott

Jonathan Wojtkowiak

David Basanta

Genomics

Gregory Kryukov

Broad Institute

Shamil Sunyaev

BWH Genetics

Tug-of-war between driver and passenger mutations in cancer and other adaptive processes

Christopher D. McFarland[a], Leonid A. Mirny[a,b,c,1], and Kirill S. Korolev[b,d,1]

TUMOUR EVOLUTION *Nature Reviews Cancer* | AOP, published online 7 March 2013; doi:10.1038/nrc3488

Weighed down by passengers?